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Vascular Alterations in Connective Tissue Disease

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Many facets of the problem of arteritis in relation to hypersensitivity are highly controversial and since I have made no specific studies in this connection, this presentation will be largely based upon an evaluation of the literature and personal experience.

Periarteritis nodosa was first recognized about 90 years ago. The medium-sized muscular arteries were involved, with a predisposition for the splanchnic area. Few lesions of terminal arterioles or veins were noted and the pulmonary vessels escaped.

After 1925, the concept that the disease was a hypersensitive reaction to a non-toxic agent grew, and seems now to be almost universally accepted, although the offending antigen in many cases remains obscure.

Friedberg and Gross[1] (1934) described four cases of periarteritis nodosa in which there was typical rheumatic carditis as evidenced by Aschoff bodies. It is easy to be wise in retrospect, but can we not now explain the findings in these cases on the basis of rheumatic fever alone? Gross considered several other cases of polyarteritis to have an associated rheumatic fever, but these were not included because they did not fulfill his rigid criteria for a diagnosis of rheumatic fever. He expressed the opinion that the association of these two conditions was more frequent than was generally recognized.

A most significant advance was that of Rich[2], with the observation of polyarteritis in five patients dying of serum sickness, four of whom had received sulfa drugs so that it was necessary to consider the factor of drug sensitivity. His report stimulated much experimental work, on the basis of which hypersensitivity has been established as the principal factor in the production of necrotizing arteritis, presumably the result of an antigen-antibody combination at some site within, or adjacent to, the vascular wall.

The case for hypersensitivity as a causative factor is supported by the observation that bronchial asthma is frequently complicated by vascular alterations such as one observes in polyarteritis[3]. Looking at the problem in reverse, of 300 cases of polyarteritis, 54 (or 18 per cent) had asthma (described as allergic granulomatosis). Wegener's granulomatosis is another condition in which there is a destructive lesion of the respiratory tract, arteritis and nephritis.

The labelling of such entities as granulomatous may be helpful from a clinical standpoint, yet I fail to see much advantage because the basic pathologic alteration of these two conditions (allergic and Wegener's granulomatosis) is primarily a vascular one. The wide variability of response in different cases would seem to signify quantitative differences modified by such

factors as the duration of illness, nature of the antibody response, the antigen-antibody ratio and the level of sensitization of the host. Most workers find it advantageous to designate cases associated with allergy as hypersensitivity arteritis or angitis, and to separate them from classical polyarteritis, the principal difference being that in the former condition (hypersensitivity arteritis) the small vessels—arteries, veins, as well as capillaries—are involved, and the pulmonary vessels are not exempt. I have never analyzed our cases to check this point, but am of the opinion that when tissues are widely examined in all cases, there are frequent exceptions to this pattern.

Although great emphasis has been placed on hypersensitivity in the pathogenesis of arteritis, other significant factors may operate in the various forms of vascular disease under discussion. Such factors as hypertension, the administration of certain steroids, or large amounts of sodium, might each appropriately be discussed at length. I will mention only one point in this connection. A recent observation by Campbell and Santos-Buch[4] indicates that in the rabbit there are differences between the vascular lesions incited by sensitization with horse serum when contrasted with those produced by constricting one kidney with silk, followed by contralateral nephrectomy. In these experiments the vascular alterations preceded the development of hypertension and did not correlate with it.

Of interest in the light of current therapy are the findings in the vascular system of patients with rheumatoid arthritis, a disease not usually associated with hypersensitivity, but for which one can make a strong case. A recent report[5] has attributed three deaths to vascular lesions associated with gangrene of the extremities in patients receiving steroid therapy. The histologic findings presented are indistinguishable from those observed in polyarteritis. For the five year period, 1953 to 1957 inclusive, the deaths of 36 patients with rheumatoid arthritis and arteritis attributed to steroid therapy have been reported.

Before incriminating therapy, the status of the blood vessels prior to the use of steroids must be considered. It is known that a variety of vascular lesions may occur in the synovial membrane, coronary arteries or skeletal muscles of patients with rheumatoid arthritis.

Sokoloff, Wilens and Bunim[6] (1951) described arteritis in the striated muscles of five of 57 cases of rheumatoid arthritis who had never received steroids. They pointed out that rheumatoid arteritis is unlike periarteritis in several significant respects. In 1957, a report[7] on ten cases noted the increasing frequency of the condition and the possibility that some of the alterations resulted from the deleterious effect of steroid therapy. They emphasized the wide spectrum of lesions and now noted some of their cases to be indistinguishable from periarteritis nodosa.

Bywaters[8] has described peripheral vascular disease in the extremities of seven patients with rheumatoid arthritis who had never received steroids. If steroid therapy does aggravate the vascular lesions, and the evidence suggests that it does, there is need for greater precaution in treatment, even though steroids have a known beneficial effect upon polyarteritis.

(The findings in three cases were presented to illustrate the points discussed. These included the autopsy findings on a patient with rheumatoid arthritis and extensive vascular alterations, and a fatal case of thrombotic thrombocytopenic purpura attributable to formalin sensitivity; also a patient with a history of rheumatic fever, tuberculosis, and drug sensitivity whose biopsy revealed necrotizing vascular alterations.)

I would like to diverge for a bit and report upon a recent observation by Dr. Hartmann[9] of our department. During a study on carcinogenicity of various fluorinated derivatives of 10 methyl 1,2 benzanthracene (10-Me-BA), all rats injected subcutaneously with the 4'-fluoro derivative died within eight weeks. Conspicuous alterations were observed in the vessels of the lungs and kidneys of these animals.

The lesions were first observed in the lungs of a rat killed two weeks after injection of 4'-fluoro-10-Me-Ba. By the fourth week four of seven animals had advanced lesions in the pulmonary and/or renal ves-

sels, and all but one killed thereafter had lesions. The larger branches of the pulmonary and bronchial arteries are involved. The media is edematous and infiltrated with polymorphonuclear leukocytes and fibroblasts. Necrosis usually involves segments of the vessel walls. In the kidneys the conspicuous alteration is hyaline necrosis of the afferent arterioles, which occasionally involves a portion of or the entire glomerulus. Lesions are reminiscent of those seen in malignant hypertension.

The renal lesions were most pronounced at four and five weeks, but absent after seven and eight weeks. This suggests that the lesion is reversible. Hawn and Janeway[10] observed regression of vascular lesions induced in rabbits by the administration of foreign proteins; such regression was correlated with a decreased level of circulating antigen.

The lack of such lesions in rats given the parent hydrocarbon 10-Me-BA or the 3-fluoro derivative would tend to exclude a toxic effect, as would the delay in development. Such a delay in development strongly suggests that chemical sensitivity is the principal etiologic factor. Sensitization to 9,10 dimethyl-1,2-benzanthracene has been reported following topical application in a human volunteer.

Various polycyclic aromatic hydrocarbons have been shown to combine with certain tissue proteins of the mouse *in vivo*. Should the 4′-fluoro-10-Me-benzanthracene compound likewise combine with one or more proteins *in vivo* and yield an antigenic foreign protein, auto-immunization would result. I have cited this experiment for two reasons: 1) Such an experiment may give us another entering wedge with which to explore the pathogenesis of arteritis under controlled experimental conditions. 2) It should also alert us as pathologists to the possibility of an increasing development of arteritis in patients currently receiving a battery of chemotherapeutic as well as other chemical agents.

From the foregoing it is evident that the vascular lesions in a wide variety of conditions result from a reaction of antigen and antibody, and although the basic mechanism may be similar, different degrees of reactivity result in a wide variety of tissue alterations. Some are acute and fulminating, with or without eosinophilia; some have an intense plasma cell reaction indicative of antibody response. Others resemble granulomata with giant cell reaction. Ultimately, as the process subsides, reparative fibrosis predominates.

I do not wish to minimize microscopic morphology, yet it seems that perhaps we are focussing too intently upon this phase of the problem. If forced to place the above conditions into separate categories on the basis of microscopy alone, most of us might fare rather badly. This indicates that there are few, if any, specific anatomic characteristics by which such lesions can be accurately separated. In other words, there are sufficient similarities to suggest that the alterations in each condition, although due to different etiologies, are produced by somewhat similar mechanisms.

Let us look at vascular disease in general and then at arteritis in particular. There seems to be little question that arteriosclerosis is a man-made disease, that is, if one accepts the fact that diet, stress and genetics are significant. In the case of arteritis we apparently have another such disease. Since the time of Jenner, foreign proteins have been injected into man. During the early days of immunization large amounts of horse serum were administered.

High-priced stocks of pharmaceutical houses are a reflection of the amount of chemicals being administered as drugs, many of which are capable of combining with proteins to act as potential sensitizing antigens in susceptible individuals. Although the present danger from such toxicants is considerable, it may be much greater for subsequent generations.

What are the responsibilities of the pathologist in this problem? Since we alone make the definitive diagnosis, we have some contact with all cases of arteritis and therefore have an unusual opportunity to follow the course with repeat biopsies and at necropsy. We also uncover the nonsuspected case in surgical specimens or from the postmortem examination, as in cases that I have cited. Because of our unique relationship with all medical services, we

are probably most familiar with the increasing incidence of this group of diseases and should so inform the profession.

I should also like to make a plea for more extensive investigative interest in this area by pathologists, utilizing the newer tools at hand. Fluorescent antibody and isotope techniques seem to offer certain opportunities. This is a problem that will require a broad knowledge of immunology, biochemistry and genetics for its solution, yet it would seem that ultimately an insight into tissue structure and cytology will also be of paramount interest. Of all scientists, the pathologist seems admirably equipped to solve the problem. The greatest need, however, is for bright young men with energy, enthusiasm and imagination.

*Experimental Coronary Thrombosis and Myocardial Infarction Induced by Diet in Rats**

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We have previously reported a dietary method for the production of arterial thrombi and infarcts in rats involving the feeding of semi-synthetic diets that included large amounts of fat, cholesterol, propylthiouracil and bile salts as basic ingredients[11, 12]. One of the diets (containing 40 per cent butter) used in the original experiments has been repeated in six subsequent experiments with an over-all incidence of infarcts varying from 7 per cent to 60 per cent (average 20 per cent). However, when only those rats that survive for two months are considered, the incidence of infarction is much more constant (average 27 per cent). In addition, 38 modifications of the above diet have been fed to separate groups of rats. Many of these have resulted in a similar incidence of infarcts; others in a lower incidence or absence of infarcts; none in a clearly higher incidence. In substitution experiments, diets containing either butter, lard or Crisco (along with other basic ingredients) have had a similar high incidence, but diets containing large amounts of corn oil (otherwise plus the same basic ingredients) have produced practically no infarcts. In omission experiments, no single ingredient has been found to be absolutely essential for the production of infarcts, but the absence of any of the basic ingredients has resulted in a drastically lowered incidence.

Cholesterol levels in the blood rise rapidly in rats on all of the infarct-producing diets, but levels have not been significantly higher in those with infarcts than in those without. Further chemical studies are planned.

A method has been developed for the study of clot-lysis in rats on infarct-producing diets utilizing the thromboelastograph. Under the conditions of the experiment it has been demonstrated that clots from rats on certain of the infarct-producing diets (containing butter) lyse more slowly than those from rats on similar diets in which corn oil is substituted for butter. Experiments with the thromboelastograph are being expanded in work now in progress with Drs. R. F. Scott and A. S. Daoud in an effort to identify the specific hematologic alteration and the specific chemical factor that causes the alteration.

It is our belief that arterial thrombosis in man and animals results from the interplay of two factors: 1) a local factor, usual-

* The experiments reviewed herein were done in collaboration with Drs. W. S. Hartroft and R. M. O'Neal of Washington University in St. Louis and with the aid of PHS grants H-1820 and H-4727.

ly atherosclerosis, and 2) a hematologic factor, either procoagulative or antifibrinolytic or both. In the experiments reported herein we believe that the principal effect has been on the hematologic factor.

DISCUSSION

SIGMUND L. WILENS: I want to start by saying that I admired Dr. Angevine's scholarly and logical presentation of the various types of non-infectious, allergic arteritis, and I find I can hardly take exception to any of the major opinions that he expressed. This will not make for a lively discussion, since I do not have any objections to what he said, but I might elaborate just a little bit on the arterial lesions he described in association with rheumatoid arthritis. Dr. Sokoloff[13], at the time he was studying the focal lymphocytic accumulations in muscle, which were considered to be specific for rheumatoid arthritis, made a rather extensive study in which he cut muscle biopsies in serial section and stained every fifth section, so that we ended up with 300 or 400 slides from each block, and of these we found only one or two had any arterial lesions at all. It is obvious, therefore, that at least in the pre-steroid era, it was like looking for a needle in a hay-stack to find these lesions. They did not have the severity of the lesions Dr. Angevine found. His lesions outshadowed ours by far. Many of us have seen the bizarre type of case of rheumatoid arthritis which, while under heavy steroid therapy, suddenly develops systemic disease with marked arterial involvement and granulomatous lesions of the spleen and other organs, producing a picture which is not unlike Wegener's granulomatosis without the kidney lesions. I have no explanation for it other than to suggest that some new type of hypersensitivity comes into play, and I have no further comment to make.

Regarding Dr. Angevine's statement that all of these vascular processes belong in the same group, and that we are probably not justified in attempting to segregate them too sharply, in general, I agree with that too. I think, however, there are patterns of lesions that fall into fairly distinct groups. Dr. Angevine mentioned the work recently reported from Cornell[4, 14] in which the arterial lesions produced in rabbits by massive injections of horse serum differed from those of experimental hypertension. When I was an interne in pathology I was working under Drs. Pappenheimer and von Glahn, who were studying arteritic lesions that they found in certain cases of active rheumatic fever. They felt that this lesion was different from the lesion of periarteritis nodosa, although I think they were hard put to it to describe what the difference was. They believed, however, that in rheumatic arteritis, no matter how severe the inflammatory process in the arterial wall might be, the lumen almost never became thrombosed. In other words, they felt it was not the endothelium of the vessels that was attacked, but it was the extracellular substances of the vessel wall. In periarteritis nodosa, however, thrombosis is a common complication. It is interesting that in the inflammatory lesions produced by Rich[15], and since then by a host of others, by intravenous injection of massive amounts of horse serum into rabbits, the intense inflammatory lesions which develop, in coronary arteries particularly, also do not become thrombosed. This, to my mind, puts them a little more in the category of the lesions of rheumatic disease rather than periarteritis nodosa. I feel it is justified to separate these two.

As I say, I enjoyed Dr. Angevine's presentation. After all, he is a pathologist of my own vintage; he speaks the same language that I do. The coinage of new words that have come into the pathological vocabulary in recent years is sometimes quite distressing, and it is gratifying that Dr. Thomas did not use the word "infarctoid" in his presentation. I was rather afraid that he might, not that he is responsible for coining that word. In any case, I think the presentation of Dr. Thomas, if I may turn to that now, is more exciting because it is newer, and I think it is more controversial.

About 50 years ago, when the first successful experimental production of dietary arteriosclerosis was reported[16], the average pathologist was not willing to accept it at all. He was so deeply imbued with the idea

that arteriosclerosis was a degenerative disease that he could not accept the concept that it could be produced by feeding animals special diets. The pathologists at that time interposed many objections to the idea that this experimental lesion was at all comparable to human arteriosclerosis. I think through the years we have seen some of these objections answered. Originally this dietary lesion was thought to be a peculiarity of the rabbit. Later, Forest Kendall[17], taking advantage of the fact that thiouracil would slow down metabolism, was able to produce the same lesion in dogs by combining cholesterol feeding with thiouracil. More recently, Rosenman, Byers and Freedman[18] reported that the feeding of cholesterol and bile salts to rats at the same time would cause a fairly decent elevation of blood cholesterol to about 200 to 250 mg. per cent. Shortly thereafter, Fillios and the Boston group under Dr. Stare decided to combine all three procedures[19]. Rats under this triple regimen did develop severe hypercholesterolemia and eventually atherosclerosis, and in a very few instances, I believe, they developed myocardial infarcts. I do not know how comparable those few infarcts are to yours, Dr. Thomas. Also Dr. Deming[20], working at Goldwater Memorial Hospital, has used the triple threat, if you will permit me to call it that, plus making his animals hypersensitive by putting a clip on one renal artery, and when he does this, he increases the severity of the atherosclerotic lesion in the rats. After three or four months he found a fair percentage of myocardial infarcts, though he tells me this varies with the strain of the rats used. In some instances the incidence was comparable to some reported by you, Dr. Thomas. For example, in one experiment, five in a group of 30 developed infarcts. In the Deming experiment, the cardiac lesions were more conventional, in the sense that they were associated with occlusive atherosclerotic lesions in the coronary arteries, which I gather Dr. Thomas did not find.

Dr. Thomas's findings introduce a brand-new concept in the pathogenesis of myocardial infarcts. The arteriosclerotic lesion itself, although it might be an inciting factor, would not appear to be a necessary precursor to myocardial infarction, according to your findings. I think it should also be pointed out that when we feed cholesterol to a rabbit, we do get lipid deposits in the coronary arteries, but the appearance of the arteries is strikingly different from the appearance of the coronary artery in human atherosclerosis, and myocardial infarcts do not develop. I do not think anyone would deny that. The lipid does not stay in the intima of the coronary artery of the rabbit. We find it permeating through the media and causing increased thickening of the vessel wall, but this increased thickness affects only the external diameter. The vessel becomes thicker on the outside, but the lumen remains the same in size, whereas in human atherosclerosis the lipid deposits are confined to the intima. It is true that in the experimental atherosclerotic lesion the lipid does penetrate more deeply into the media than is usually seen in human spontaneous atherosclerosis, but this may be related to the intensity of the process and the tremendous elevation of blood cholesterol, which is associated with these lesions. This is in sharp contrast to what is usually seen in man. In any case, the production of infarcts in this one species, the rat, I think, has removed another major obstacle to accepting the idea that myocardial infarction may be related to dietary habits, such as the consumption of large amounts of cholesterol and other materials.

In preparing for this discussion I read Dr. Thomas's original paper[12] which appeared about two years ago, and also a manuscript of a paper now in press, which he was good enough to send me. On reading these, a number of questions occurred to me about the nature of the infarction and of the vascular lesion which I hoped he might answer in his presentation tonight, but Dr. Thomas has probably repeated this material so many times that he was more interested in talking about his more recent studies. I have prepared a number of questions concerning the nature of these vascular lesions and cardiac lesions which I think might help me, at least, and possibly other pathologists, who try to interpret the significance of Dr. Thomas's results in terms

of human infarction. You may say you are not primarily interested in that at the moment and yet a comparison of the two lesions is inevitable. I do not think it would be cricket, however, for me to ask questions about data which Dr. Thomas did not present here, do you, Dr. Zimmerman?

H. M. ZIMMERMAN: No, I do not think it would be cricket.

SIGMUND L. WILENS: I agree it would not be fair to ask questions on material not presented here, so I shall not do so.

QUENTIN BURRITT DEMING: I would like to ask Dr. Thomas two questions. The first is, what do the rats who die in the first few months die of? What sort of state are these animals in? The second question is relevant to the fascinating data you were presenting on the technique for measuring the lysis of the clot. You presented the cholesterol levels by groups. They were at extraordinary heights, and the group with the highest cholesterol had the longest clot lysis time. I wonder whether you know what the correlation was between the lysis time and the cholesterol level. What I am getting at is this: is it conceivable that this technique is merely measuring something directly related to plasma lipid?

WILBUR A. THOMAS: It is even harder to say in these rats what they die of than it is in man; I do not know what the rats die of at any time in these experiments, with the exception of about 10 per cent who died of infection. The rats for the most part are immature, weighing 100 grams (at maturity on a normal diet they should weigh 400 grams) and with thiouracil alone they will stop growing. The weight stays about the same throughout the experiments. The rats do not look well; they are not in good condition; they are at the verge of the absolute limit they will tolerate, because whenever we tried to raise the incidence of the lesions by increasing any factor in the diet, all the rats would die in a short time, so we knew we were giving them a "bad" diet. For the most part we could not tell what the rats died of; they die without anatomic lesions to explain the death, except that they had fatty livers, and so on. One very curious thing, or perhaps not curious, but one of the facts, was that the rats with infarcts lived just as long as the rats without infarcts. When we averaged the duration of life after the beginning of each experiment, we found that those who had infarcts lived as long as those who did not have infarcts. Many of the infarcts were large enough so that they might have caused death, or at least we would have expected them to in man.

In regard to your other question, we have no information on which to base an answer. What I presented were the only positive results we have gotten so far. The blood cholesterol levels in the rats in our experiments on infarct-producing diets were around the 2000 mg. per cent range, whether or not the rats had infarcts. All we were measuring was cholesterol, but obviously many other lipid elements were increased; at the time, cholesterol was all we knew how to measure in our tissue laboratory. The plasma looked like melted butter in many of these animals. As to which one of the elements in the diet or blood produces the effect on lysis we do not know. Our next step is to try to find out the specific chemical factor or factors that are involved.

RICHARD M. TORACK: Have you tested the blood of ulcer patients who are on Sippy diets to determine if there is prolonged lysis of clots?

WILBUR A. THOMAS: No, we have not. We would like to, and we would also like to test the blood of Uganda natives, who have virtually no infarcts, against our Albany citizens, who appear to have the highest incidence of infarcts in any part of the country, but we have not done anything about it as yet. One thing Dr. Wilens said I would like to comment on. Perhaps I expressed myself poorly, but I did not intend to imply that I am not interested in man. What I wanted to say is that I do not feel we are warranted as yet in drawing conclusions in regard to man from these experiments. However, we are working with rats because we are interested in man.

HENRY G. SCHMIDT, JR.: I would like to know if any of your vascular occlusions were related to intrinsic disease of the blood vessel walls. Did you have occlusions related to vascular lesions?

WILBUR A. THOMAS: No thrombotic occlusions could be related to specific local vascular lesions. Some fat was present in all coats of arteries everywhere, but no real plaque formation. We did serial sections of these hearts, and before I left St. Louis, as a matter of interest, I counted how many sections had been cut, and it was something over 20,000 sections. We used the carbowax technique, which makes it possible to do fat stains on anything you want in serial sections, and we did four different stains. I saw no connection with any local lesion in the vessel wall with thrombosis in any single animal. I saw fat in vessel walls, and saw fat in the thrombi, wherever they occurred, but I did not see any more fat in the vessel walls at the site of thrombosis than elsewhere, nor in thrombi than in ordinary postmortem clots in these rats. We looked at tissues with the light microscope, the phase microscope, and the electron microscope, and have seen no local lesion in the vessel walls that explains the thrombus in any terms that we understand in man. I think we are mainly doing something to the clotting systems in these animals. Fat is present in the arterial walls and it is possible that the fat in the vessel wall has *something* to do with the thrombosis, but I am convinced that the main effect is on the blood itself in these animals.

GEORGE E. MURPHY: Do fat stains of the heart reveal any fatty alteration in heart muscle cells in the rats in your experiments?

WILBUR A. THOMAS: In the infarcts we saw fat, of course, and the more fat the animal got, the more fat we saw in the infarcts. In the muscle away from the infarct we did not see fatty change. I might make one comment here about "infarctoid", since Dr. Wilens used that term. We called the lesions in our rats infarcts because we think they are infarcts; they look like infarcts, and not like foci of necrosis from other causes. I have done experiments in which we injected streptokinase and also infected animals with hemolytic streptococci and produced multiple areas of necrosis in the myocardium; also we gave massive doses of vitamin D and produced multiple areas of necrosis in the myocardium, but mostly small, focal lesions, "metabolic lesions", if you will. I do not think that we are producing "metabolic lesions" in the animals described tonight. We usually found only single lesions having the configuration of infarcts; we did not find multiple areas of necrosis or degeneration or anything else. The muscle in the areas, except for the infarct, looked all right.

JAMES I. BERKMAN: May I ask Dr. Angevine one question? Regarding the rats with arterial necrosis, were these animals hypertensive?

D. MURRAY ANGEVINE: No measurements of blood pressure were made on these animals. On the basis of the histology of the vasculature in the kidney one might expect that there was some degree of hypertension. In view of the probable reversibility of these lesions it would be of considerable interest to investigate them further from the standpoint of altered renal physiology.

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